[REPLACEMENT SHEET]

Intravascular Delivery of Non-Viral Nucleic Acid

This application is a Continuation-In-Part of the following: U.S. Serial No. 09/707,000 filed on November 6, 2000, U.S. Serial No. 09/707,117 filed on November 6, 2000, U.S. Serial No. 09/450,315 filed on November 29, 1999, U.S. Serial No. 09/000,533 filed on December 30, 1997, U.S. Serial No. 09/070,303 filed on April 30, 1998, U.S. Serial No. 08/571,536 filed on December 13, 1995, and U.S. Serial No. 09/391,260 filed on September 7, 1999, which is a Continuation of Issued Patent No. 6,265,387 filed on December 13, 1995.

Field of the Invention

The invention relates to compounds and methods for use in biologic systems. More particularly, processes that transfer nucleic acids into cells are provided. Nucleic acids in the form of naked DNA or a nucleic acid combined with another compound are delivered to cells.

Background

Biotechnology includes the delivery of a genetic information to a cell to express an exogenous nucleotide sequence, to inhibit, eliminate, augment, or alter expression of an endogenous nucleotide sequence, or to express a specific physiological characteristic not naturally associated with the cell. Polynucleotides may be coded to express a whole or partial protein, or may be anti-sense.

A basic challenge for biotechnology and thus its subpart, gene therapy, is to develop approaches for delivering genetic information to cells of a patient in a way that is efficient and safe. This problem of "drug delivery," where the genetic material is a drug, is particularly challenging. If genetic material are appropriately delivered they can potentially enhance a patient's health and, in some instances, lead to a cure. Therefore, a primary focus of gene therapy is based on strategies for delivering genetic material in the form of nucleic acids. After delivery strategies are developed they may be sold commercially since they are then useful for developing drugs.

Delivery of a nucleic acid means to transfer a nucleic acid from a container outside a mammal to near or within the outer cell membrane of a cell in the mammal. The term transfection is used herein, in general, as a substitute for the term delivery, or, more specifically, the transfer of a nucleic acid from directly outside a cell membrane to within the cell membrane. The transferred (or transfected) nucleic acid may contain an expression cassette. If the nucleic acid is a primary RNA transcript that is processed into messenger RNA, a ribosome translates the messenger RNA to produce a protein within the cytoplasm. If the nucleic acid is a DNA, it enters the nucleus where it is transcribed into a messenger RNA that is transported into the cytoplasm where it is translated into a protein. Therefore if a nucleic acid expresses its cognate protein, then it must have entered a cell. A protein may subsequently be degraded into peptides, which may be presented to the immune system.

It was first observed that the in vivo injection of plasmid DNA into muscle enabled the expression of foreign genes in the muscle (Wolff, J A, Malone, R W, Williams, P, et al. Direct gene transfer into mouse muscle *in vivo*. *Science* 1990;247:1465-1468.). Since that report, several other studies have reported the ability for foreign gene expression following the direct injection of DNA into the parenchyma of other tissues. Naked DNA was expressed following its injection into cardiac muscle (Acsadi, G., Jiao, S., Jani, A., Duke, D., Williams, P., Chong, W., Wolff, J.A. Direct